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*Original Article*

# A Periodic Stem Cells Population Model with State-Dependent Delay

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***Abstract*** *- Granulocyte colony-forming stimulating factor (G-CSF) is a frequently indicated medication for the treatment of leukopenia. In order to investigate the effect of cyclic G-CSF injection on the population dynamics of HSCs, a cyclic hematopoietic HSCs (HSCs) population model was investigated. The model is composed of an ordinary differential equation with periodic coefficients and a partial differential equation, which can be transformed into a phase-structure model with state-dependent delay by means of the characteristic line method. First of all, the linearization is performed at the zero solution, the Poincaré mapping and the spectral radius of the linearized system are defined, the threshold R0 is obtained, and the global dynamics of the system is analyzed. The results show that when* $R_0 < 1$*, the zero solution is attracted globally, which indicates that the cells would become extinct. When* $R_0 > 1$*, a positive periodic solution exists whereby the system is consistently persistent, so the cells will not disappear but will always exist.*

***Keywords*** *- Cell differentiation, HSCs, Periodic solutions, Size-structured population models, State-dependent delay.*

## 1. Introduction

HSCs are mainly distributed in bone marrow and can be divided into dormant HSCs and dividing HSCs. HSCs can self-proliferate and differentiate into different types of blood cells through mitosis, such as erythrocytes, leukocytes and blood platelets. The functions of the different types of blood cells are described in detail in [1-4].

The hematopoietic system is a complex nonlinear regulatory system [5]. Under normal conditions, various regulatory factors interact to maintain the relative stability of blood cell morphology and number. However, due to the change of some regulatory parameters, the number of blood cells will show a significant wide range of fluctuations, which are clinically manifested as a variety of different dynamic blood diseases. For example, cyclic leukopenia, cyclic thrombocytopenia and so on. Periodic injections of G-CSF are usually used in the treatment of leukopenia [6]. Since the generation of various blood cells is derived from the differentiation of HSCs, it is necessary to deactivate the dynamics of HSCs. The dynamics of HSCs will be regulated by the feedback of mature blood cells. When the dynamics of blood cells are abnormal, the corresponding population dynamics of HSCs will also be affected.

Periodic injection of G-CSF can be used to treat cyclic leukopenia and alleviate the side effects of chemotherapy, and also produce corresponding periodic feedback and regulation of HSCs population. This chapter considers the dynamic behavior of HSCs population during periodic injection of G-CSF.

For the remainder of this paper the organization is as follows. The rest of this chapter is organized as follows. In Section 2, a dynamic model of the proliferation and differentiation of HSCs is established. In Section 3, the model is transformed into a model with state-dependent delay by solving the partial differential equation. In this case, the delay depends on the amount of dormant HSCs and is adjusted by the feedback of the amount of HSCs in the diapause period. In order to discuss the adaptability of the solution, the state-dependent delay model is transformed into a differential equation with constant delay by time variable transformation. The threshold of the established model is analyzed in Section 4. The Poincare mapping and spectral half-path are defined according to the linearized system at the zero solution, and the threshold $R_0$ is obtained. The global dynamics of the system are analyzed according to the relationship between the threshold $R_0$ and 1. Finally, this chapter is summarized in Section 5.

## 2. Model Formulation

We consider a population of HSCs and classify them into resting HSCs and proliferating HSCs according to their status in the bone marrow. The number of resting HSCs at time $t$ is denoted by $h(t)$, and $s(q,t)$ is used to express the distribution density of proliferating HSCs with maturity $q$ at time $t$, so that the overall number of all proliferating HSCs with maturity between $q_1$ and $q_2$ at time $t$ is

$$\int_{q_1}^{q_2} s(q,t)dq.$$

We restrict $q \in [0,\sigma]$, where $\sigma$ denotes the final maturity level of proliferating HSCs. Therefore, $s(t,0)$ means that the HSCs starts to enter the proliferative phase from the resting phase, $s(t,q)$, $q>0$ means that the proliferating HSCs, correspondingly $s(t,\sigma)$ means that the proliferative cell division is completed, and one cell can divide into two cells and start to enter the resting phase. We hypothesis that the maturation rate $g$ would be dependent on the amount of dormant HSCs [7]. In [8], nutrients are thought to be regulators of the length of the cell cycle. Nutrients incorporate with the cell and alter the concentration of proteins in the cell. These nutrients bind to the cell and alter the concentration of proteins within the cell, determining the stage of the cell cycle phases. Assuming that the concentration of nutrient supply is constant, the rate of maturation of proliferating cells is a function of the increasing amount of nutrients available to each non-proliferating cell, so $g$ is a reducing function of $h(t)$. The greater the number of dormant HSCs, the smaller $g$ will be, and the slower the maturation rate of proliferating HSCs. The function g is then considered to be positive, bounded, continuously differentiable, and mono-decreasing. We define

$$g_0 = \sup_{x\geq 0} g(x) = g(0), \quad g_{\sigma in} = \inf_{x\geq 0} g(x).$$

The proliferating HSCs die at a certain rate of $\gamma \geq 0$, and after a period of mitosis they reach maturity $\sigma$ and immediately split into two daughter cells and come to the rest phase.

The resting HSCs are introduced into the proliferative phase at a certain rate $\beta$, $\beta$ relies on the number of resting HSCs [9]. $\beta$ is positive, bounded, continuously differentiable, singly decreasing, and $\lim_{x\to+\infty}\beta(x)=0$. In general, it is assumed that the function $\beta$ is a monotonically decreasing Hill function [9], as follows

$$\beta(x) = \frac{\beta_0 \rho^\alpha}{\rho^\alpha + x^\alpha},$$

where, $\beta_0 \geq 0$, $\rho > 0$ and $\alpha > 0$. The differentiation rate of the resting HSCs depends on the overall number of corresponding mature cells in the cycle. Assuming that the feedback of the number of erythrocytes and platelets to the resting HSCs is fixed, the differentiation rate of the resting HSCs is only affected by the change in the number of leukocytes, $K(t)$, which varies with the number of leukocytes. G-CSF is commonly used in the treatment of leukopenia [5], and is usually injected periodically in order to suppress the side effects of chemotherapy on cancer patients. In this case, the number of leukocytes will show cyclical changes, and therefore, $K(t)$ is a cyclical function. The development of the HSCs population can be given by the equation

$$\begin{cases} \frac{dh(t)}{dt} = 2g\big(h(t)\big)s(t,\sigma) - \Big(\beta\big(h(t)\big) + K(t)\Big)h(t), \\ \partial_t s(t,q) + g\big(h(t)\big)\partial_q s(t,q) = -\gamma s(t,q), \\ g\big(h(t)\big)s(t,0) = \beta\big(h(t)\big)h(t), \end{cases} \tag{1}$$

given the initial function $s(0,q) = s_0(q)$, $h(0) = h_0$, where the continuous function $K(t)$ is $\omega$-periodic, $h_0$ is a non-negative real number, and $s_0(q)$ is a non-negative continuous function on$[0,\sigma]$.

## 3. Reduction to a Delay Differential Equation

Using the characteristic line method [10-14], it can be verified that the solution for $s(t,q)$ is

$$s(t,q) = \begin{cases} s_0\left(q - \int_0^t g\big(h(r)\big)dr\right)e^{-\gamma t}, & (t,q) \in E_1, \\ \frac{\beta\big(h(t-\tau(q,h_t))\big)}{g\big(h(t-\tau(q,h_t))\big)}h\big(t-\tau(q,h_t)\big)e^{-\gamma\tau(q,h_t)}, & (t,q) \in E_2, \end{cases} \tag{2}$$

where

$$E_1 = \left\{(t,q): 0 \le q \le \sigma, \int_0^t g\big(h(r)\big)dr < q \right\},$$
$$E_2 = \left\{(t,q): 0 \le q \le \sigma, \int_0^t g\big(h(r)\big)dr \ge q \right\}.$$

For $(t,q) \in E_1$, substituting $s(t,\sigma)$, defined by (2), into (1) gives a non-autonomous equation

$$\frac{dh(t)}{dt} = 2g\big(h(t)\big)s_0\left(\sigma - \int_0^t g\big(h(r)\big)dr\right)e^{-\gamma t} - \Big(\beta\big(h(t)\big) + K(t)\Big)h(t).$$

For $(t,q) \in E_2$, the solution of model (1) satisfies a delay system

$$\frac{dh(t)}{dt} = \frac{2g(h(t))\beta\big(h(t-\tau(\sigma,h_t))\big)e^{-\gamma\tau(\sigma,h_t)}}{g\big(h(t-\tau(\sigma,h_t))\big)}h\big(t-\tau(\sigma,h_t)\big) - \Big(\beta\big(h(t)\big) + K(t)\Big)h(t), \tag{3}$$

where the delay is state-dependent and is defined by the implicit function

$$\sigma = \int_{t-\tau(\sigma,h_t)}^{t} g(h(r))dr,$$

and satisfies

$$\frac{\partial\tau}{\partial t} = 1 - \frac{g(h(t))}{g\big(h(t-\tau(\sigma,h_t))\big)}.$$

In order to investigate the fitness of the solution, we make a time-invariant state-dependent change, for $t > 0$,

$$\hat{t} = \int_0^t g(h(r))dr,$$
$$\hat{h}(\hat{t}) = h(t), \ \ \hat{K}(\hat{t}) = K(t).$$

Then the system (3) is converted to

$$\frac{d\hat{h}(\hat{t})}{d\hat{t}} = \frac{2\beta\big(\hat{h}(\hat{t}-\sigma)\big)e^{-\gamma\hat{\tau}\left(\sigma,\hat{h}_{\hat{t}}\right)}}{g\big(\hat{h}(\hat{t}-\sigma)\big)}\hat{h}(\hat{t}-\sigma) - \frac{1}{g(\hat{h}(\hat{t}))}\big(\beta\big(\hat{h}(\hat{t})\big) + \hat{K}(\hat{t})\big)\hat{h}(\hat{t}), \tag{4}$$

where

$$\hat{\tau}\big(\sigma,\hat{h}_{\hat{t}}\big) = \int_{\hat{t}-\sigma}^{\hat{t}} \frac{1}{g(\hat{h}(\theta))}d\theta.$$

For $t \in [-\sigma, 0]$, the corresponding initial condition is

$$\hat{h}(t+\sigma) = \hat{\phi}(\hat{t}),$$

where $\hat{\phi}(\hat{t}) \in \mathcal{C}[-\sigma, 0]$.

## 4. Threshold Dynamics

The next generation matrix method is used to introduce the threshold $R_0$ of model (4).

For any continuous $\omega$-periodic function $k(t)$, let $\overline{k} = \max\limits_{t\in[0,\omega]} k(t)$, $\underline{k} = \min\limits_{t\in[0,\omega]} k(t)$. Firstly, the suitability of the solution of the system (4) is discussed. Make $X = \mathcal{C}([-\sigma, 0], \mathbb{R})$, $X^+ = \mathcal{C}([-\sigma, 0], \mathbb{R}_+)$.

Theorem 4.1: As for any $\hat{\varphi} \in X^+$, there is a unique non-negative solution $\hat{h}(\hat{t}, \hat{\varphi})$ of system (4) satisfying $\hat{h}_0 = \hat{\varphi}$, and the solution is also eventually bounded for all $\hat{t} \ge 0$.

Proof: For any $\hat{\varphi} \in X^+$, we define

$$\hat{f}(\hat{t}, \hat{\varphi}) = \frac{2\beta(\hat{\varphi}(-\sigma))e^{-\gamma\hat{\tau}\left(\sigma,\hat{\varphi}(0)_{\hat{t}}\right)}}{g(\hat{\varphi}(-\sigma))} - \frac{1}{g(\hat{\varphi}(0))}\big[\beta\big(\hat{\varphi}(0)\big) + \hat{K}(\hat{t})\big]\hat{\varphi}(0).$$

Note that $\hat{f}(\hat{t}, \hat{\varphi})$ is consecutive in $(\hat{t}, \hat{\varphi}) \in \mathbb{R}_+ \times X^+$, from the properties of $g$, $\beta$ and $K$ given above it follows that $\hat{f}(\hat{t}, \hat{\varphi})$ is Lipschitz in $\hat{\varphi}$ on each tight subset of $X^+$. From [15], the system (4) then has a single solution $\hat{h}(\hat{t}, \hat{\varphi})$ on its maximum existence interval with $\hat{h}_0 = \hat{\varphi}$.

Note that $\hat{h}(\hat{t}) = 0$ is always the solution of the equation (4). Since $\hat{\varphi}$ is a positive function, by using the existence and uniqueness of solutions, we can get that $\hat{h}(\hat{t}) > 0$ is always valid.

From the boundedness of the functions $K$ and $g$, we have

$$\frac{d\hat{h}(\hat{t})}{d\hat{t}} = \frac{2\beta\left(\hat{h}(\hat{t}-\sigma)\right)e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g\left(\hat{h}(\hat{t}-\sigma)\right)}\hat{h}(\hat{t}-\sigma) - \frac{1}{g\left(\hat{h}(\hat{t})\right)}\left(\beta\left(\hat{h}(\hat{t})\right) + \widehat{K}(\hat{t})\right)\hat{h}(\hat{t})$$
$$< \frac{2\beta\left(\hat{h}(\hat{t}-\sigma)\right)e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\hat{h}(\hat{t}-\sigma) - \frac{1}{g_0}\left(\beta\left(\hat{h}(\hat{t})\right) + \underline{\widehat{K}}\right)\hat{h}(\hat{t}). \tag{5}$$

Assume that $\frac{2\beta(0)e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}} \geq \underline{\widehat{K}}$. Since $\beta$ is decreasing and $\lim_{\hat{h}\to\infty}\beta(\hat{h}) = 0$, there is a unique $\hat{h}_0 \geq 0$ such that

$$\frac{2\beta(\hat{h}_0)e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}} = \underline{\widehat{K}},$$

and

$$\frac{2\beta(\hat{h})e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}} = \underline{\widehat{K}}, \qquad \hat{h} \geq \hat{h}_0. \tag{6}$$

If $\frac{2\beta(0)e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}} < \underline{\widehat{K}}$, then (6) holds with $\hat{h}_0 = 0$. Set

$$\hat{h}_1 := \frac{2e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\frac{\beta(0)\hat{h}_0}{\underline{\widehat{K}}} \geq 0.$$

One can check that

$$\frac{2e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\max_{0\leq\hat{y}\leq\hat{h}}\beta(\hat{y})\hat{y} \leq \underline{\widehat{K}}\hat{h}, \quad \text{for } \hat{h} \geq \hat{h}_1. \tag{7}$$

Indeed, let $\hat{y} \in [0, \hat{h})$. If $\hat{y} \leq \hat{h}_0$, then

$$\frac{2e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\beta(\hat{y})\hat{y} \leq \frac{2e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\beta(0)\hat{h} = \underline{\widehat{K}}\hat{h}_1 \leq \underline{\widehat{K}}\hat{h},$$

and, if $\hat{y} > \hat{h}_0$, then

$$\frac{2e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\beta(\hat{y})\hat{y} \leq \underline{\widehat{K}}\hat{y} \leq \underline{\widehat{K}}\hat{h}.$$

Hence, (7) holds.

Assume, by contradiction, that $\lim_{\hat{t}\to\infty}\max\hat{h}(\hat{t}) = +\infty$, where $\hat{h}(\hat{t})$ is a solution of (4). Then, there exists $\hat{t}_0 > \sigma$ such that

$$\hat{h}(\hat{t}) \leq \hat{h}(\hat{t}_0), \qquad t \in [\hat{t}_0 - \sigma, \hat{t}_0], \qquad \hat{h}(\hat{t}_0) > \hat{h}_1.$$

With (7), we obtain that

$$\frac{2e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\beta\left(\hat{h}(\hat{t}_0-\sigma)\right)\hat{h}(\hat{t}_0-\sigma) \leq \underline{\widehat{K}}\hat{h}(\hat{t}_0).$$

This yields, with (5), that

$$\frac{d\hat{h}(\hat{t})}{d\hat{t}} \leq \frac{2\beta\left(\hat{h}(\hat{t}-\sigma)\right)e^{-\gamma\hat{\tau}(\sigma,\hat{h}_{\hat{t}})}}{g_{\sigma in}}\hat{h}(\hat{t}-\sigma) - \frac{1}{g_0}\left(\beta\left(\hat{h}(\hat{t})\right) + \underline{\widehat{K}}\right)\hat{h}(\hat{t})$$
$$\leq \frac{1}{g_0}\beta\left(\hat{h}(\hat{t}_0)\right)\hat{h}(\hat{t}_0)$$
$$< 0,$$

which gives a contradiction. Hence, $\lim_{\hat{t}\to\infty}\max\hat{h}(\hat{t}) < +\infty$, The proof of Theorem 4.1 is comepleted.

Linearizing the system (4) at $\hat{h} \equiv 0$ yields the following linear system

$$\frac{d\overline{\hat{h}}(\hat{t})}{d\hat{t}} = \hat{q}(\hat{t})\overline{\hat{h}}(\hat{t}-\sigma) - \hat{b}(\hat{t})\overline{\hat{h}}(\hat{t}), \tag{8}$$

where $\hat{q}(\hat{t}) = \frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}}$ and $\hat{b}(\hat{t}) = \frac{1}{g(0)}(\beta(0) + \widehat{K}(\hat{t}))$.

Let $G\colon \mathbb{R} \to \mathfrak{L}(X, \mathbb{R})$ is a mapping besides $S(\hat{t})$ is a continuous function on $\mathbb{R}$, as given below

$$G(\hat{t})\hat{\varphi} = \hat{q}(\hat{t})\hat{\varphi}(-\sigma), \qquad S(\hat{t}) = \hat{b}(\hat{t}).$$

So the linear system (8) could be reduced to

$$\frac{dm(\hat{t})}{d\hat{t}} = G(\hat{t})m_{\hat{t}} - S(\hat{t})mm(\hat{t}).$$

In this case, the newly generated resting HSCs are described by $G(\hat{t})$. In addition to this, the internal evolution of resting hematopoietic HSCs, such as differentiation, is represented by the following evolutionary system

$$\frac{dm(\hat{t})}{d\hat{t}} = -S(\hat{t})m(\hat{t}).$$

Let $\Gamma(\hat{t},\hat{z})$, $\hat{t} \geq \hat{z}$, be an evolutionary operator for the linear system described above, which means that $\Gamma(\hat{t})$ is satisfied with

$$\frac{\partial}{\partial \hat{t}}\Gamma(\hat{t},\hat{z}) = -S(\hat{t})\Gamma(\hat{t},\hat{z}), \quad \forall \hat{t} \geq \hat{z}, \quad \Gamma(\hat{z},\hat{z}) = I, \quad \forall \hat{z} \in \mathbb{R}.$$

It then easily follows that

$$\Gamma(\hat{t},\hat{z}) = e^{-\int_{\hat{z}}^{\hat{t}} \hat{b}(r)dr}, \qquad \forall \hat{t} \geq \hat{z}, \qquad \hat{z} \in \mathbb{R}.$$

Such that $X_{\hat{\omega}}$ is the ordered Banach space for all $\hat{\omega}$-periodic continuity functions from $\mathbb{R}$ to $\mathbb{R}$, fitted with a maximal norm. The correct cone $X_{\hat{\omega}}^{+} = \{\hat{m} \in X_{\hat{\omega}} : \hat{m}(\hat{t}) \geq 0,\ \hat{t} \in \mathbb{R}\}$.

Suppose that $\hat{m} \in X_{\hat{\omega}}$ is the initial distribution of non-proliferating hematopoietic HSCs in the cyclic environment. Then for any given $\hat{z} \geq 0$, $G(\hat{t}-\hat{z})_{\hat{t}-\hat{z}}$ is the distribution of newly proliferating resting hematopoietic HSCs at time $\hat{t}-\hat{z}$. Then $\Gamma(\hat{t},\hat{t}-\hat{z})G(\hat{t}-\hat{z})\hat{m}_{\hat{t}-\hat{z}}$ is the distribution of cells that were newly added at time $\hat{t}-\hat{z}$ remained alive at time $\hat{t}$. It follows that

$$\int_0^{\infty} \Gamma(\hat{t},\hat{t}-\hat{z})G(\hat{t}-\hat{z})\hat{m}_{\hat{t}-\hat{z}}\,d\hat{z} = \int_0^{\infty} \Gamma(\hat{t},\hat{t}-\hat{z})G(\hat{t}-\hat{z})\hat{m}(\hat{t}-\hat{z}+\cdot)d\hat{z},$$

is the distribution of the accumulation of new cells produced from the past moment to moment $\hat{t}$.

The next generation operator $L: X_{\hat{\omega}} \to X_{\hat{\omega}}$, which we define as

$$[L\hat{m}](\hat{t}) = \int_0^{\infty} \Gamma(\hat{t},\hat{t}-\hat{z})G(\hat{t}-\hat{z})\hat{m}(\hat{t}-\hat{z}+\cdot)d\hat{z}, \quad \forall \hat{t} \in X_{\hat{\omega}}.$$

According to [16-19], then we define $R_0 = r(L)$, the spectrum radius of $L$. For $\hat{t} \geq 0$, $P(\hat{t})$ is the solution map of system (8), in the sense that $P(\hat{t})\hat{\psi} = \hat{m}_{\hat{t}}(\hat{\psi})$, for which $\hat{m}(\hat{t},\hat{\psi})$ is the only solution of the system (8) with $\hat{m}_0 = \hat{\psi} \in X$. Then we have $P := P(\hat{\omega})$ is the Poincaré (period) map about the linear system (8). Suppose that $r(P)$ be the spectrum radius of $P$. Taking into account [16], we obtained the following results.

**Lemma 4.1:** $R_0 - 1$ and $r(P) - 1$ have the same sign.

**Lemma 4.2:** $P(\hat{t})$ is an $\hat{\omega}$-periodic semiflow on $X^{+}$, i.e. $(i)\ P(0) = I$, $(ii)\ P(\hat{t}+\hat{\omega}) = P(\hat{t}) \circ P(\hat{\omega})$ for all $\hat{t} \geq 0$, and $(iii)\ P(\hat{t})\hat{\phi}$ is continuous in $(\hat{t},\hat{\phi}) \in [0,\infty) \times X^{+}$. Next, it is shown that the solution map $P(\hat{t})$ is s ultimately strongly monotone.

**Lemma 4.3:** For any $\hat{\varphi}$ and $\hat{\psi}$ in $X^{+}$ with $\hat{\varphi} > \hat{\psi}$, (i.e. $\hat{\varphi} \geq \hat{\psi}$ but $\hat{\varphi} \neq \hat{\psi}$), the solutions $\overline{\hat{m}}(\hat{t}) = \hat{m}(\hat{t},\hat{\varphi})$ and $\hat{m}(\hat{t}) = \hat{m}(\hat{t},\hat{\psi})$ of system (8) with $\overline{\hat{m}}_0 = \hat{\varphi}$ and $\hat{m}_0 = \hat{\psi}$, respectively, satisfying $\overline{\hat{m}}(\hat{t}) > \hat{m}(\hat{t})$ for all $\hat{t} \geq \sigma$, so that, $P(\hat{t})\hat{\varphi} \gg P(\hat{t})\hat{\psi}$ in $X^{+}$ for all $\hat{t} \geq 2\sigma$.

**Proof**: We first show that $\overline{\hat{m}}(\hat{t}_0) > \hat{m}(\hat{t}_0)$ for some $\hat{t}_0 \in [0.\sigma]$. Assume, by contradiction, that $\overline{\hat{m}}(\hat{t}) = \hat{m}(\hat{t})$ for all $\hat{t} \in [0,\sigma]$. Then $\frac{d\overline{\hat{m}}(\hat{t})}{d\hat{t}} = \frac{dm(\hat{t})}{d\hat{t}}$ for all $\hat{t} \in (0,\sigma)$, and hence,

$$\frac{d\overline{\hat{m}}(\hat{t})}{d\hat{t}} = \frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}}\overline{\hat{m}}(\hat{t}-\sigma) - \frac{1}{g(0)}(\beta(0)+\hat{K}(\hat{t}))\overline{\hat{m}}(\hat{t}),$$
$$\frac{d\hat{m}(\hat{t})}{d\hat{t}} = \frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}}\hat{m}(\hat{t}-\sigma) - \frac{1}{g(0)}(\beta(0)+\hat{K}(\hat{t}))\hat{m}(\hat{t}),$$

that is,

$$\frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}}\left[\overline{\hat{m}}(\hat{t}-\sigma) - \hat{m}(\hat{t}-\sigma)\right] = 0, \quad \forall \hat{t} \in [0,\sigma].$$

It follows that $\overline{\hat{m}}(\hat{t}-\sigma) - \hat{m}(\hat{t}-\sigma)$ for all $\hat{t} \in [0,\sigma]$, we have $\hat{\varphi}(\hat{\theta}) = \hat{\psi}(\hat{\theta})$ for all $\hat{\theta} \in [-\sigma,0]$, which contradicts the assumption that $\hat{\varphi} > \hat{\psi}$ in $X^{+}$.

Let

$$g(\hat{t},\hat{\xi}) := \frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}}\hat{m}(\hat{t}-\sigma) - \frac{1}{g(0)}(\beta(0)+\hat{K}(\hat{t}))\overline{\hat{\xi}}(\hat{t}).$$

Since $\frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}} \geq 0$, then for all $\hat{t} \geq \hat{t}_0$,

$$\frac{d\overline{\hat{m}}(\hat{t})}{d\hat{t}} = \frac{2\beta(0)}{g(0)}e^{-\gamma\frac{\sigma}{g(0)}}\overline{\hat{m}}(\hat{t}-\sigma) - \frac{1}{g(0)}(\beta(0)+\hat{K}(\hat{t}))\overline{\hat{m}}(\hat{t})$$

$$\geq \frac{2\beta(0)}{g(0)} e^{-\gamma \frac{\sigma}{g(0)}} \widehat{m}(\hat{t}-\sigma) - \frac{1}{g(0)}(\beta(0)+\hat{K}(\hat{t}))\overline{\widehat{m}}(\hat{t})$$
$$= g(\hat{t}, \overline{\widehat{m}}(\hat{t})),$$

and hence,

$$\frac{d\overline{\widehat{m}}(\hat{t})}{d\hat{t}} - g\left(\hat{t}, \overline{\widehat{m}}(\hat{t})\right) \geq 0 = \frac{d\widehat{m}(\hat{t})}{d\hat{t}} - g\left(\hat{t}, \widehat{m}(\hat{t})\right), \quad \forall \hat{t} \geq \hat{t}_0.$$

Since $\overline{\widehat{m}}(\hat{t}_0) > \widehat{m}(\hat{t}_0)$, the comparison theorem of ordinary differential equations from [19] means that $\overline{\widehat{m}}(\hat{t}) > \widehat{m}(\hat{t})$ for all $\hat{t} \geq \hat{t}_0$. Since $\hat{t}_0 \in [0, \sigma]$, $\overline{\widehat{m}}(\hat{t}) > \widehat{m}(\hat{t})$ for all $\hat{t} \geq \sigma$, and hence, $P(\hat{t})\hat{\varphi} \gg P(\hat{t})\hat{\psi}$ for all $\hat{t} \geq 2\sigma$. The demonstration of Lemma 4.3 is completed.

Let $Q(\hat{t})$ be the solution maps of system (4) on $X^+$, i.e., $Q(\hat{t})\hat{\phi} = \hat{h}_{\hat{t}}(\hat{\phi})$, $\hat{t} \geq 0$, where $\hat{h}(\hat{t}, \hat{\phi})$ is the unique solution of system (4) satisfying $\hat{h}_0 = \hat{\phi} \in X^+$. With a discussion similar to that of [20], we obtain the following consequence.

**Lemma 4.4:** $Q(\hat{t})$ is an $\widehat{\omega}$-periodic semiflow on $X^+$ i.e., $(i)$ $Q(0) = I$, $(ii)$ $Q(\hat{t}+\widehat{\omega}) = Q(\hat{t}) \circ Q(\widehat{\omega})$ for all $\hat{t} \geq 0$, and $(iii)$ $P(\hat{t})\hat{\phi}$ is continuous in $(\hat{t}, \hat{\phi}) \in [0, \infty) \times X^+$.

We now certify the main consequence of this section.

**Theorem 4.2:** $(i)$ In the event that $r(P) < 1$, the solution $\hat{h} \equiv 0$ is globally attracted in $X$. $(ii)$ In the event that $r(P) > 1$, there exists a positive $\widehat{\omega}$-periodic solution $\hat{h}^*(\hat{t})$ of system (4) and there is a real number $\eta > 0$ so that the solution $\hat{h}(\hat{t}, \hat{\phi})$ satisfies $\lim_{\hat{t}\to\infty} \min \hat{h}(\hat{t}, \hat{\phi}) \geq \eta$ for any $\hat{\phi} \in X^+$.

**Proof**: Since $\frac{2\beta(0)}{g(0)} e^{-\gamma \frac{\sigma}{g(0)}} > 0$, it follows from [21] and [22] that for each $\hat{t} \geq 2\sigma$, the linear operator $P(\hat{t})$ is compact and strong positive on $X$. Select one integer $n_0 > 0$ so that $n_0\widehat{\omega} \geq 2\sigma$. Due to $P^{n_0} = P(n_0\widehat{\omega})$, [23] means that $r(P)$ is a simple eigenvalue of $P$ with a strong positive eigenvector and that any other eigenvalue has a modulus smaller than $r(P)$. Let $\mu = \frac{ln\ r(P)}{\widehat{\omega}}$. It follows from [16] that there exists a positive $\widehat{\omega}$-periodic function $\widehat{w}(\hat{t})$ so that $\hat{h}(\hat{t}) = e^{\mu\hat{t}}\widehat{w}(\hat{t})$ which is a positive solution of linear equation (8).

With $r(P) < 1$, we have $\mu = \frac{ln\ r(P)}{\widehat{\omega}} < 0$. Select a sufficiently great number $M > 0$ to make $\hat{h}(\hat{t}) \leq M\hat{h}(\hat{t})$, $\forall \hat{t} \geq n_0\widehat{\omega} - \sigma$. Therefore, the comparison theorem for delay differential equations [22] suggests that

$$\hat{h}(\hat{t}) \leq M\hat{h}(\hat{t}) = Me^{\mu\hat{t}}\widehat{w}(\hat{t}), \quad \forall \hat{t} \geq n_0\widehat{\omega}.$$

and as a result, $\lim_{\hat{t}\to\infty} \hat{h}(\hat{t}) = 0$. This supports statement $(i)$.

With $r(P) > 1$, we would apply the persistence theory of periodic semi-flows. $X_0 = \{\hat{\phi} \in X: \hat{\phi}(0) > 0\}$ and $\partial X_0 := X \backslash X_0 = \{\hat{\phi} \in X: \hat{\phi}(0) = 0\}$. Let $Q(\hat{t})\hat{\phi} = \hat{h}_{\hat{t}}(\hat{\phi})$, $\forall \hat{\phi} \in X$. Then $Q := Q(\widehat{\omega})$, is the Poincaré map related to system (4) on $X$ and $Q^n = Q(n\widehat{\omega})$, $\forall n \geq 0$.

It follows from the equation (4), it is not difficult to see that $Q(\hat{t})X_0 \subseteq X_0$ for all $\hat{t} \geq 0$. By Theorem 1, the discrete-time system $Q^n: X \to X_{n\geq 0}$ is point dissipative. By [15], for each $\hat{t} \geq \sigma$, $Q(\hat{t})$ is compact, and thus $Q^n$ is tight for adequately great $n$. From [7] it can be seen that $Q$ has a strong global attractor in $X$. Next, we show that $Q$ is uniformly persistent for $(X_0, \partial X_0)$.

Let $M_1 = 0$, then $Q(M_1) = M_1$. Since $\lim_{\hat{\phi}\to M_1} \left\| Q(\hat{t})\hat{\phi} - Q(\hat{t})M_1 \right\| = 0$ uniformly for $\hat{t} \in [0, \widehat{\omega}]$, there exists $\eta_1(\varepsilon)$ such that for any $\hat{\phi} \in X_0$ with $\left\|\hat{\phi} - M_1\right\| < \eta_1$, we have $\left\| Q(\hat{t})\hat{\phi} - Q(\hat{t})M_1 \right\| < \varepsilon$ for all $\hat{t} \in [0, \widehat{\omega}]$. We further have the below claim.

Claim: $\lim_{n\to\infty} \max \left\| Q^n\hat{\phi} - M_1 \right\| \geq \eta_1$, for all $\hat{\phi} \in X_0$. This means that $M_1$ is the isolated invariant set of $Q$ in $X$, $W^l(M_1) \cap X_0 = \emptyset$, where $W^l(M_1)$ is not an unstable set of $M_1$ for $Q$. Let $\partial X_0 = X \backslash X_0$, and

$$M_\partial = \hat{\phi} \in \partial X_0: Q^n\hat{\phi} \in \partial X_0, \quad \forall n \geq 0.$$

Since

$$\frac{d\hat{h}(\hat{t})}{d\hat{t}} \geq -\frac{1}{g\left(\hat{h}(\hat{t})\right)}\left(\beta\left(\hat{h}(\hat{t})\right) + \hat{K}(\hat{t})\right)\hat{h}(\hat{t}), \quad \hat{t} \geq 0,$$

It is easy to get that if for some $\hat{t}_0 > 0$, there is $\hat{h}(\hat{t}_0) > 0$, then $\hat{h}(\hat{t}) > 0$ for all $\hat{t} \geq \hat{t}_0$. This property means for $\forall \hat{t} \geq 0$, as long as the $\hat{\phi} \in M_\partial$, have $\hat{h}(\hat{t}) = 0$. Then with respect to $\partial X_0$, $M_1$ cannot form a cycle with respect to $Q$. Based on the acyclic theorem of mapping uniform persistence (see [24]), $Q: X \to X$ is uniformly persistent about $X_0$. As a result, it follows from [24]

that the periodic semi-flow $Q(\hat{t}: X \to X)$ is also uniformly persistent with about $X_0$ . By an argument similar to the proof in [25], we show the existence of positive $\hat{\omega}$-periodic solutions of the system (4) and the persistence of the system.

Since the coefficients are periodic, we only show the existence, and the threshold $R_0$ here is an abstraction value.

## 5. Conclusion

In this paper, we propose a model for the proliferation and differentiation of haematopoietic HSCs populations, distinguishing between dormant and proliferating HSCs according to their status in the bone marrow. Proliferating HSCs can undergo mitosis and random death, and the duration of mitosis of these cells is regulated by regulatory factors secreted by dormant HSCs. Dormant HSCs are capable of differentiation, and when G-CSF is injected periodically, the differentiation rate of dormant HSCs changes periodically, and the aim of the study is to investigate the effect of this periodicity on HSCs population dynamics.

Firstly, solving partial differential equations using the characteristic line method, and the system is transformed into a state-dependent delay model. Since the equations are decoupled, we only discuss the dynamics of the resting HSCs population. By linearizing the zero solution, the Poincare mapping and spectral radius of the linear system are defined, and then the threshold $R_0$ is obtained. When $R_0 < 1$, the zero is globally attractive and the cells become extinct. When $R_0 > 1$, the system has a positive periodic solution and uniform persistence is proved, indicating that the cells will always exist, but the uniqueness of the positive periodic solution is not obtained.

## References


[1] C. Colijn, and M. C. Mackey, "A Mathematical Model of Hematopoiesis: II. Cyclical Neutropenia," *Journal of Theoretical Biology*, vol. 237, no. 2, pp. 133-146, 2005. *Crossref*, https://doi.org/10.1016/j.jtbi.2005.03.034

[2] C. Foley, and M. C. Mackey, "Dynamic Hematological Disease: A Review," *Journal of Mathematical Biology*, vol. 58, no. 1, pp. 285-322, 2009. *Crossref*, https://doi.org/10.1007/s00285-008-0165-3

[3] L. Israels, and E. Israels, 3rd Ed, "*Mechanisms in Hematology*," Core Health Services, 2002.

[4] C. Zhuge, J. Lei, and M. C. Mackey, "Neutrophil Dynamics in Response to Chemotherapy and G-CSF," *Journal of Theoretical Biology*, vol. 293, no. 4, pp. 111-120, 2012. *Crossref*, https://doi.org/10.1016/j.jtbi.2011.10.017

[5] M. Adimy, F. Crauste, and S. Ruan, "A Mathematical Study of the Hematopoiesis Process with Applications to Chronic Myelogenous Leukemia," *SIAM journal on applied mathematics*, vol. 65, no. 4, pp. 1328-1352, 2005.

[6] S. Basu, G. Hodgson, and M. Katz, "Evaluation of Role of G-CSF in the Production, Survival, and Release of Neutrophils from Bone Marrow into Circulation," *Blood*, vol. 100, no. 3, pp. 854-861, 2002. *Crossref*, https://doi.org/10.1182/blood.v100.3.854

[7] J. Kirk, J. S. Orr, and J. Forrest, "The Role of Chalone in the Control of the Bone Marrow HSCS Population," *Mathematical Biosciences*, vol. 6, no. 4, pp. 129-143, 1970.

[8] T. Alarcon, and M. J. Tindall, "Modelling Cell Growth and its Modulation of the G1/S Transition," *Bulletin of Mathematical Biology*, vol. 69, no. 1, pp. 197-214, 2007. *Crossref*, https://doi.org/10.1007/s11538-006-9154-0

[9] M. C. Mackey, "Unified Hypothesis for the Origin of Aplastic Anemia and Periodic Hematopoiesis," *Blood*, vol. 51, no. 5, pp. 941-956, 1978. *Crossref*, https://doi.org/10.1182/blood.V51.5.941.941

[10] J. Bélair, and J. M. Mahaffy, "Variable Maturation Velocity and Parameter Sensitivity in a Model of Haematopoiesis," *Mathematical Medicine and Biology*, vol. 18, no. 2, pp. 193-211, 2001.

[11] C. Colijn, and M. C. Mackey, "A Mathematical Model of Hematopoiesis-I. Periodic Chronic Myelogenous Leukemia," *Journal of Theoretical Biology*, vol. 237, no. 2, pp. 117-132, 2005. *Crossref*, https://doi.org/10.1016/j.jtbi.2005.03.033

[12] H. L. Smith, "A Structured Population Model and a Related Functional Differential Equation: Global Attractors and Uniform Persistence," *Journal of Dynamics and Differential Equations*, vol. 6, no. 1, pp. 71-99, 1994. *Crossref*, https://doi.org/10.1007/BF02219189

[13] H. L. Smith, "Equivalent Dynamics for a Structured Population Model and a Related Functional Differential Equation," *The Rocky Mountain Journal of Mathematics*, vol. 25, no. 1, pp. 491-499, 1995. *Crossref*, https://doi.org/10.1216/rmjm/1181072298

[14] Y. Lv, R. Yuan, and Y. He, "Wavefronts of a Stage Structured Model with State--Dependent Delay," *Discrete and Continuous Dynamical Systems*, vol. 35, no. 10, pp. 4931-4954, 2015. *Crossref*, https://doi.org/10.3934/dcds.2015.35.4931

[15] J. K. Hale, and S. M. V. Lunel, "*Introduction to Functional Differential Equations*," Springer Science and Business Media, vol. 99, 2013.

[16] X. Q. Zhao, "Basic Reproduction Ratios for Periodic Compartmental Models with Time Delay," *Journal of Dynamics and Differential Equations*, vol. 29, no. 1, pp. 67-83, 2017. *Crossref*, https://doi.org/10.1007/s10884-015-9425-2

[17] F. Li, and X. Q. Zhao, "A Periodic SEIRS Epidemic Model with a Time-Dependent Latent Period," *Journal of Mathematical Biology*, vol. 78, no. 5, pp. 1553-1579, 2019. *Crossref*, https://doi.org/10.1007/s00285-018-1319-6

[18] W. Wang, "Global Behavior of an SEIRS Epidemic Model with Time Delays," *Applied Mathematics Letters*, vol. 15, no. 4, pp. 423-428, 2002. *Crossref*, https://doi.org/10.1016/S0893-9659(01)00153-7

[19] T. Zhang, and Z. Teng, "On a Nonautonomous SEIRS Model in Epidemiology," *Bulletin of Mathematical Biology*, vol. 69, no. 8, pp. 2537-2559, 2007. *Crossref*, https://doi.org/10.1007/s11538-007-9231-z

[20] W. Walter, "On Strongly Monotone Flows," *Annales Polonici Mathematici*, vol. 66, no. 3, pp. 269-274, 1997. *Crossref*, http://eudml.org/doc/269959

[21] Y. Lou, and X. Q. Zhao, "A Theoretical Approach to Understanding Population Dynamics with Seasonal Developmental Durations," *Journal of Nonlinear Science*, vol. 27, pp. 573-603, 2017. *Crossref*, https://doi.org/10.1007/s00332-016-9344-3

[22] L. Smith, "*Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*," American Mathematical Social, 1995.

[23] D. Xu, and X. Q. Zhao, "Dynamics in a Periodic Competitive Model with Stage Structure," *Journal of mathematical analysis and applications*, vol. 311, no. 2, pp. 417-438, 2005. *Crossref*, https://doi.org/10.1016/j.jmaa.2005.02.062

[24] X. Q. Zhao, "*Dynamical Systems in Population Biology*," Springer, 2003.

[25] Y. Lou, and X. Q. Zhao, "Threshold Dynamics in a Time-Delayed Periodic SIS Epidemic Model," *Discrete and Continuous Dynamical Systems-B*, vol. 12, no. 1, pp. 169-186, 2009. *Crossref*, https://doi.org/10.3934/dcdsb.2009.12.169